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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,035	02/09/2001	Tariq Ghayer	BBC-084	8433

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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,035	GHAYER ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12 and 14-61* is/are pending in the application.

4a) Of the above claim(s) *39-43 and 47-60* is/are withdrawn from consideration.

5)☒ Claim(s) *37 and 38* is/are allowed.

6)☒ Claim(s) *4-12, 14-36, 44-46 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4-12 and 14-61* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 20 May 2004 is acknowledged and entered. Following the amendment, claims 22, 29-31, and 36-38 are amended.

Currently, claims 4-12 and 14-61 are pending, and claims 4-12, 14-38, 44-46 and 61 are under consideration.

Withdrawal of Objections and Rejections:

The rejection for lack of written description, and the scope rejection of claims 37 and 38 under 35 U.S.C. 112, first paragraph, are withdrawn in view of applicant's amendment and argument.

Formal Matters:

Claims 39 and 44 are objected to as being dependent upon a canceled claim, claim 13. The applicant is required to rewrite the claims in independent form including all of the limitations of the base claim and any intervening claims, or to amend the claims to depend on a pending claim.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 29, 36 and their dependent claims 23-28, 32-35, and 39-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not specifically pointed out (other than "this amendment is supported throughout the specification as filed"), nor can the Examiner locate, the basis in the specification

for the new limitation of "at least *two* variable regions" in the amended claims 22, 29, 36, respectively.

This is a new matter rejection.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-36 remain rejected, and the dependent claims 39-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the previous Office Actions.

Applicants argument filed on 20 May 2004 has been fully considered, but is not deemed persuasive for reasons below.

At page 12 of the response, the applicant argues that it is unclear why the Examiner has rejected claims 30, 31, 37 and 38, since the claimed antibody, or an antigen binding portion thereof encompass six CDRs. This argument is not persuasive because, with exception of claims 37 and 38 that recite the sequence structure of an antibody light chain (SEQ ID NO:29), claims 30 and 31 recite "a light chain variable region having an amino acid sequence of SEQ ID NO:15 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:16 (or 17)", which merely represent a small portion (11 or 17 amino acids in length), but not three CDRs of a light or a heavy chain. As such, even though claims 30 and 31 *encompass* six CDRs by reciting "a light chain *variable region* and a heavy chain *variable region*", the sequence structure of at least three CDRs of one antibody chain is not defined. Therefore, a skilled artisan cannot envision the detailed chemical structure of the encompassed antibody or an antigen-binding portion thereof comprising SEQ ID NO:15 and 16 (or 17), and would not be able to make said antibody or an portion thereof capable of binding human IL-18.

Claims 22-36 remain rejected, and the dependent claims 39-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies and antigen-binding fragments thereof, in which the three CDRs in the heavy chain variable region or the three CDRs in the light chain variable region are all defined by a single antibody, and which bind the relevant antigen (human IL-18 or a peptide epitope thereof), and for mutants of these antibodies in which a limited number of defined changes are made in one or more CDRs; does not reasonably provide enablement for antibodies and antigen-binding fragments thereof that comprise *less than three* heavy chain CDRs or three light chain CDRs defined by the amino acid sequence of a parental antibody that binds the same antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons of record set forth in the previous Office Actions, and for the same reasons above.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-12, 14-24, 44-46 and 61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al. (US6,075,181, of record) and Dinarello et al. (J. Leukoc. Biol. 1998, 63:658-664. IDS #A4), for the reasons of record set forth in the previous Office Actions.

Applicants argument filed on 20 May 2004 has been fully considered, but is not deemed persuasive for reasons below.

At page 14 of the response, the applicant argues that, by the Examiner's own admission, the cited references, neither singularly or in combination, teach, suggest, or motivate one skilled in the art to produce a human antibody capable of neutralizing the activity of human IL-18, that the Examiner has failed to provide any actual evidentiary motivation to combine the cited references as required by law. This argument is not persuasive because the Examiner never admitted that references *in combination* do not teach, suggest, or motivate one skilled in the art to produce a human antibody capable of neutralizing the activity of human IL-18, which is applicants own interpretation. The Examiner merely acknowledges that the Kucherlapati reference does not teach human antibodies *to IL-18*, and the Dinarello reference does not teach *human* antibodies. As addressed clearly in the 1st Office Action mailed on 25 June 2002, Kucherlapati teaches a method of producing fully human monoclonal antibodies to *any protein* of interest, but *especially cytokines*, and advantages of such antibodies in comparison to rodent antibodies or even humanized antibodies for therapeutic applications, as to because administration of human antibodies to humans avoiding the undesired immune responses elicited by administering non-human antibodies to humans. Additionally, Dinarello teaches that human IL-18 had been cloned and produced recombinantly (references provided), that antibodies to IL-18 can inhibit the in vivo production of other pro-inflammatory cytokines, that preventing the activity of IL-18 which induces these other cytokines is a sensible clinical strategy, and that neutralizing anti-IL-18 antibodies are a therapeutic option for specific blockade of IL-18. Therefore, even though neither Kucherlapati nor Dinarello teaches explicitly a human monoclonal antibody to human IL-18, strong suggestion or motivation to make such an antibody can be found based on combination of the references, and is instantly obvious to a person having ordinary skill in the art, that is the therapeutic application of anti-IL-18 antibody in disease

treatment (by Dinarello), and significant advantage of a human monoclonal antibody in therapeutic application in comparison to the other types of antibodies, as taught by Kucherlapati.

At page 15 of the response, the applicant argues, once again, that neither Kucherlapati nor Dinarello, singularly or in combination, teach or suggest making human antibodies to human IL-18, and that the Examiner's argument is, at best, "obvious to try" reasoning, which is improper to establish or to sustain a case of prima facie obviousness, as neither reference teaches or suggests a fully human anti-IL-18 monoclonal antibody which is actual evidence that such an approach was novel, unobvious and even unobvious to try at the time of filing the present invention. This argument is not persuasive because the combined references provide clear motivation to make such an antibody for the reasons above as this is a repeated argument. Further, with respect to the argument of unobviousness of the present invention over the prior art because *neither* reference teaches or suggests a fully human anti-IL-18 monoclonal antibody which is actual evidence, applicants attention is directed to the fact that this is not a 102 rejection, in which a single reference has to teach each and every element in a claim. In the case of obviousness rejection under 35 U.S.C. 103(a), it is the teachings of the combined references, not "neither reference", have to provide suggestion or motivation, a reasonable expectation of success, and teach or suggest all claim limitations. In the instant case, these requirements have been met by the teachings of the cited references for the reasons above. With respect to the argument of "obvious to try" reasoning by the Examiner, this is not persuasive because Kucherlapati has demonstrated successfully the production of such antibodies to multiple proteins including IL-6, IL-8 and TNF-α. Although Kucherlapati's human antibodies are not to IL-18, the expectation of success in making the presently claimed antibody was high given the state of the art, which was high in this field at the time the invention was filed, the knowledge of a person having ordinary skill in the art, and the teachings by Kucherlapati and Dinarello. Further, a *reasonable* expectation of success is not equal to a certainty of success, which is not required in the obviousness rejection under 35 U.S.C. 103(a).

At page 16 of the response, the applicant argues that patchwork compilation of art is not sufficient to establish a *prima facie* case of obviousness, and combination of this art using hindsight reconstruction is impermissible, and that in the absence of any clear and particular evidentiary showing of teaching, suggestion, or motivation to combine the cited references

establishment of a *prima facie* case of obviousness fails. This argument is not persuasive because, as addressed above, it is the teachings of the prior art references cited, which made instantly obvious to a person having ordinary skill in the art to make the presently claimed antibody as the combined references teaches clearly and particularly the potential therapeutic application of anti-IL-18 antibody in disease treatment, the advantage of human monoclonal antibodies, and the method of making such an antibody, all of which are evidentiary showing. It is such teachings, not hindsight reconstruction, provide strong motivation to combine the cited references, and an expectation of success.

Conclusion:

Claims 37 and 38 are allowable.

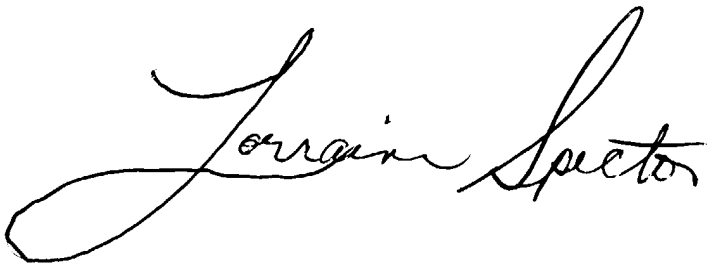
Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.



Dong Jiang, Ph.D.
Patent Examiner
AU1646
7/28/04